

Strokes, Transient Ischemic Attacks and Asymptomatic Bruits

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Research into noninvasive techniques for evaluating cerebrovascular insufficiency has shown that hemodynamically significant lesions can be identified with considerable accuracy. Concurrently, recent descriptions of carefully applied medical and surgical therapy indicate that thromboembolic stroke can be effectively prevented when patients are allocated to the proper therapeutic protocols. The approach of these two lines of basic investigation to the clinical focal point of stroke control make it imperative that clinicians review the tools at hand for identifying persons at high risk, as well as the available therapeutic alternatives for effective stroke prevention.

THE POSITION OF STROKES as one of the major public health problems facing Western civilization is based on a foundation of awesome statistics. There are more than 400,000 new cases of stroke in the United States every year, and about 40 percent of the persons so afflicted will die within 30 days. Moreover, half of the survivors will be totally disabled. In 1972 the annual cost to the country was estimated at 6.2 billion dollars.^{1,2}

In Europe there are more than 1 million new cases of stroke each year, with a 30 percent mortality as well as a 60 percent incidence of substantial disability among the survivors. In fact, only 30 percent of the survivors ever return to gainful employment. The World Health Organization has estimated that there are 1 million persons in Europe permanently disabled by a stroke, with initial hospital care costing 7 billion dollars and follow-up institutional care costing 500 million dollars a year.^{3,4}

Success in addressing this problem depends on a virtual revolution in our thinking about stroke. Cerebral stroke is in many ways analogous to a solar eclipse—a seemingly capricious and unheralded event only to the uninitiated. Although

certainly not predictable with astronomical accuracy, the inexorable progress of the atherosclerotic plaque is accompanied by a constellation of evolving signs and symptoms which offer an astute clinician many opportunities to intercede, and in contradistinction to a solar eclipse, prevent the final statistically predictable event. Indeed, it is crucial that clinicians not view stroke as an isolated entity, or according to the anachronistic description of “cerebral vascular accident,” but as one stage of disease progression in an orderly, discernible, evolutionary process ranging from the first appearance of the atherosclerotic plaque through its early clinical manifestations such as asymptomatic cervical bruits, attacks of transient cerebral ischemia and then, finally, to the fixed neurologic deficit of the completed stroke.

Although strokes are the result of a somewhat diverse group of etiologic diseases manifested by a rather sudden, and for the most part irreversible, central neurologic deficit, most occur as a consequence of progressive atherosclerotic disease. Of the entire population of patients admitted to a hospital with a diagnosis of stroke, the condition in approximately 60 percent to 70 percent of cases stems from infarction due to thromboembolism, and in 20 percent from intracerebral hemorrhage.⁴ In 5,184 men and women entered into the Framingham study over 18 years, 78

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percent of the strokes that occurred were attributable to thromboembolic disease, and of these approximately 2 percent had a known cardiac origin. Subarachnoid hemorrhage preceded the stroke in 12 percent of the patients, and intracerebral hemorrhage afflicted an additional 5 percent before the stroke. Moreover, 5 percent of the strokes were attributable to various less common illnesses.⁵

In 1919 Hunt suggested the relationship between stroke and occlusive disease in the extracranial cerebrovascular system.⁶ Subsequent epidemiologic studies substantiated these initial impressions, ascribing approximately 60 percent of all strokes to disease in the carotid and vertebral vessels. Recognition and control of disease in this region constitute the particular focus of this review.

It must be appreciated at the outset that effective therapy of stroke depends on early recognition and prophylaxis. This caveat is readily ascertained from the medical literature.^{7,8} Despite two decades of effort at establishing effective therapeutic measures once a stroke has occurred, progress remains elusive. Consequently, the mortality has not been altered during this period of various treatment regimens.⁷⁻⁹ The natural history and course of stroke have likewise remained refractory to almost every therapeutic protocol. When hemiplegia persists for 36 hours or more, the possibility of permanent incapacitating deficit is greater than 90 percent. At the end of seven days about 40 percent of the surviving patients will be neurologically stable, with another 35 percent of patients experiencing continuing neurologic improvement.^{4,7}

To reduce the dimensions of this awesome problem, the first step is to recognize the population at risk. These persons can be identified by many of the stigmata of atherosclerotic disease. Although it has not been clearly established whether these distinguishing characteristics represent true risk factors or merely coincidental associated phenomena, they serve as useful markers; their control produces well-documented salutary effects, even though the precise role in stroke prevention has not been positively identified.^{8,10-12} Each risk factor will roughly double the incidence of stroke for a similar-age but unaffected cohort in the general population,⁴ the most noteworthy being arterial hypertension as evidenced by more than 160/90 mm of mercury pressure. In the Framingham study, however, hypertensive pa-

tients had a fourfold increase in stroke incidence over the normotensive population.⁵ Radiological evidence of cardiomegaly or electrocardiographic indication of left ventricular hypertrophy or of coronary artery disease will double the incidence of stroke, as will the presence of congestive heart failure, cardiac arrhythmia or atrial fibrillation. Abnormal glucose tolerance test results, manifested by a two-hour postprandial sugar determination higher than 160 mg per dl or a fasting blood sugar greater than 120 mg per dl, are also indicators. While control of these abnormalities has become axiomatic in modern medicine, it should be appreciated that the effect of control on stroke incidence has yet to be proven.¹¹ There is evidence, however, that control of these risk factors serves to decelerate the atherosclerotic process, and one would intuitively anticipate a coincidental effect on the carotid atherosclerotic occlusive process. In addition, such factors as smoking, hyperlipidemia, diabetes, use of oral contraceptives and stress all lead to increased platelet aggregability which, as will be pointed out, are specifically pertinent to the occurrence of stroke. When any of these stigmata are encountered in a patient without symptoms of cerebrovascular disease, particular emphasis should be focused on identifying an occult carotid lesion that may be interfering with cerebrovascular hemodynamics. Moreover, it is important to realize that extracranial cerebrovascular disease can progress up to and include total occlusion of the internal carotid artery without symptomatic manifestations, until stroke occurs, seemingly without premonitory warning. Although atherosclerosis is appropriately considered a generalized disease process, there are almost invariably specific sites of predilection for stenotic lesions which give rise to the varied symptom complexes.

Physical examination of every patient in the high-risk group for stroke must give attention to the cervical pulses and include a notation as to the presence or absence of cervical bruits.

Cervical Pulses

Reduction in palpable pulse is a hallmark of atherosclerotic occlusive disease in the carotid system, and may often precede symptoms of cerebrovascular insufficiency. Measurement of blood pressure in both brachial arteries and palpation of both common carotid arteries provide valuable information about the integrity of the origin of the great vessels arising from the aortic

arch. Symmetrical blood pressure in the brachial arteries with a weak right carotid pulse generally indicates a lesion at the right common carotid origin. A weak right carotid pulse associated with an ipsilateral reduction in brachial artery pressure signifies a lesion in the innominate artery. Conversely, a reduced right brachial artery pressure with a normal right carotid pulse may serve to attribute a loud asymptomatic bruit in the neck to a subclavian lesion, with no concomitant extracranial cerebrovascular disease. Palpation of the superficial temporal artery pulses is likewise useful and a prominent enlarged superficial temporal artery is often associated with an occluded ipsilateral internal carotid artery, since the superficial temporal artery is a common collateral channel.^{13,14}

Although the enlargement of collateral vessels as a consequence of atherosclerotic occlusive disease is generally a reliable indicator of vascular occlusive pathologic conditions, a weak superficial temporal artery pulse may help to identify a lesion at the carotid bifurcation and explain a perplexing cervical bruit. Of lesions that occur in the carotid artery system, 5 percent will be identified by angiography at the aortic arch origin of the common carotid artery and 90 percent will be located at the common carotid artery bifurcation in the neck; another 5 percent will be found in that portion of the intracranial carotid artery referred to as the siphon. Surprisingly minor atherosclerotic disease is encountered elsewhere along the carotid system, even in the face of advanced occlusive lesions. Palpation of an abnormal pulse should alert clinicians to the need for further investigation.

Auscultation

Few findings on routine physical examination cause more consternation than the asymptomatic carotid bruit, yet it is a finding of consummate importance. Much has been written concerning the inaccuracy of interpreting the anatomic site or meaning of the asymptomatic cervical bruit, but a few careful maneuvers help immeasurably to evaluate these abnormal sounds correctly.¹⁵ The exercise would be only academic, however, were it not for the clinical value of recognizing this physical finding. By stepwise auscultation, the origin of a bruit can be reliably surmised. Although it would be difficult to ascribe a bruit at the angle of the jaw to internal carotid versus external carotid arteries, identification of those

bruits transmitted from the aortic arch, or arising from the vertebral or subclavian arteries, should not prove insurmountable. Numerous attempts have been made to correlate the cervical bruit with subsequent angiographic findings, and while significant stenotic lesions can be found angiographically in 50 percent of patients with cervical bruits, conversely it has been reported that approximately 20 percent of angiographically observed stenotic lesions were not associated with cervical bruits.¹⁵ Nevertheless, the recognition of a bruit is imperative, and in my experience it is unlikely that a carotid bruit can be heard without substantial pathology being identified angiographically. I am convinced that a careful clinician can distinguish bruits with far better accuracy than that reported in the medical literature, particularly when the investigator's objective was to prove the superiority of some other modality of assessment. Bruits evolve concomitantly with their plaques: from the soft, low-pitched, short-duration bruit of the moderate stenosis, to the loud, rough, prolonged systolic bruit of the 70 percent to 80 percent stenosis, to the higher-pitched, ever softer, though protracted bruits lasting into diastole, with an 80 percent to 90 percent stenosis. Finally they become barely audible and then silent as the stenosis increases beyond 95 percent.

A bruit is foreign to the neck, and when it is heard there, its origin must be clarified. "Walking" the stethoscope up the neck is the most useful way of separating the aortic outflow murmurs from carotid bruits. The carotid bifurcation bruit, which is by far the most important, increases in intensity as the angle of the mandible is approached. Bruits heard lateral to the sternocleidomastoid muscle at the root of the neck are usually subclavian or vertebral in origin.

The significance of asymptomatic bruits has been clarified by recent epidemiologic data. In studies where careful attention has been directed towards identifying bruits of cervical and, most noteworthy, carotid origin, angiographic evaluation has shown that 90 percent of asymptomatic bruits auscultated at the carotid bifurcation arise from the internal carotid artery and 10 percent from the external carotid artery. In one group of 59 patients with asymptomatic cervical bruits followed for up to eight years, 51 percent remained asymptomatic, whereas in 25 percent transient ischemic attacks occurred and in 24 percent there were frank strokes. Eleven patients went on to total internal carotid artery occlusion and in four

among them the bruits disappeared when occlusion occurred.¹⁶

Most of the patients in whom stroke developed did not have antecedent transient ischemic attacks. As a group, then, 49 percent of the patients with asymptomatic carotid bruits had either transient ischemic attacks or frank strokes during a rather brief follow-up period. Epidemiologic studies such as this have indicated the considerable significance and stroke risk that accompany an asymptomatic carotid bruit,^{16,17} but few studies have been done on the chronologic progression of cervical bruits or on the precise temporal evolution of an atherosclerotic carotid plaque. One study, however, in which cases were followed by serial angiograms, found that in 38 percent of the patients there was no demonstrable change in the size of the carotid atheromata, but in 12 percent there was a gradual increase in size; moreover, in 35 percent of the lesions, the stenosis increased at a rate faster than 25 percent per year.^{18,19}

Debate continues on the meaning and accuracy of asymptomatic cervical bruits, but no clinical data have been generated. If a bruit is not heard, nothing can be done about it; aside from recognizing that occasionally substantial arterial disease can exist in the absence of a bruit, agonizing over it will not help. Because cerebrovascular insufficiency is marked by other indicators, the absence of a bruit where it might be anticipated is interesting but minimally important. If a bruit is present, however, it represents an abnormal physical find-

ing that requires further elucidation. Within this cohort of patients, there are many in whom a stroke eventually occurs, and in a considerable number of these there will be a sudden stroke without premonitory warning.¹⁶ Inherent variation in the accuracy of clinical examination, together with the multiplicity of innocuous sources of cervical bruits added to the potential morbidity from aortic arch angiography, does not in my opinion justify routine angiography in cases of asymptomatic cervical bruits. Fortunately, noninvasive tests that are accurate, safe and moderate in cost enable clinicians to readily identify a hemodynamically significant carotid lesion as a source of the cervical bruit. These tests should be used in every case of an asymptomatic cervical bruit or an abnormal cervical pulse. If these tests are negative, reassessment should be done in the patient at yearly intervals to ascertain possible progression of a nonocclusive carotid lesion. On the other hand, if the test findings indicate a lesion of hemodynamic significance in the carotid artery system, then arteriography should be done in the patient, even though no symptoms are present. If the noninvasive test findings are positive, there is a 95 percent chance that hemodynamically significant lesions will be identified in the internal carotid artery system.

Noninvasive Cerebrovascular Tests

Although many promising tests have surfaced only to be later rejected, several simple, safe, reliable tests have gained wide acceptance over a

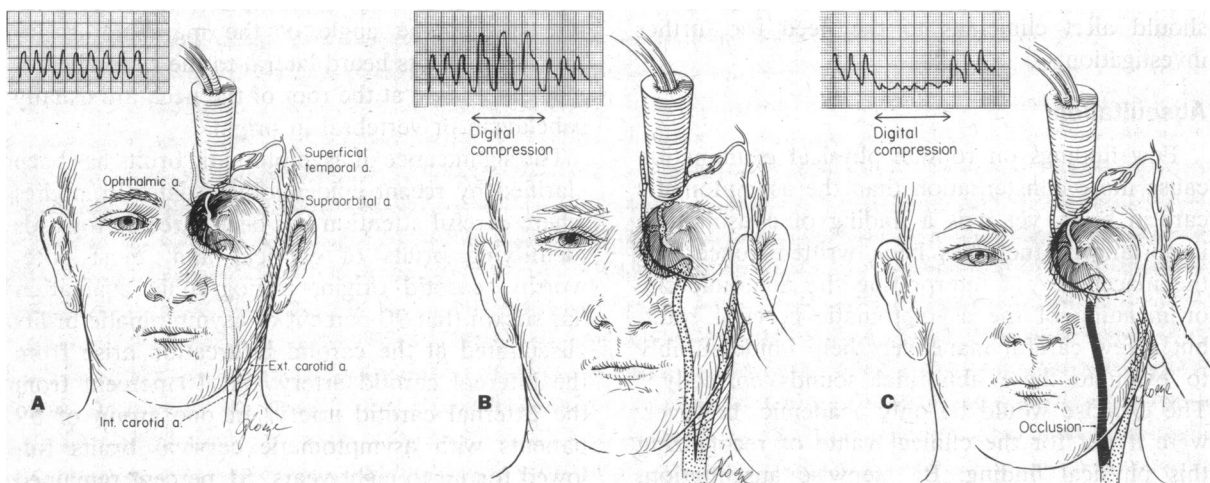


Figure 1.—A, Doppler flow meter evaluation of the supraorbital artery in the Doppler ophthalmic test; note the normal wave tracing. B, With normal internal carotid artery flow, *augmentation* is seen on the Doppler tracing of the supraorbital artery with digital compression of the superficial temporal artery. C, In the presence of hemodynamically significant stenosis, or occlusion of the internal carotid artery, the Doppler flow tracing shows obliteration of flow in the supraorbital artery upon digital compression of the superficial temporal artery.



Figure 2.—Doppler ophthalmic test being carried out.

period of time. With wide clinical application has come validation, not only under the scrutiny of investigative laboratories but also under the rigors of clinical use. Two tests that have earned the widest application and validation in the medical literature are the Doppler ophthalmic test and oculopneumoplethysmography.²⁰ The Doppler ophthalmic test has been used in our laboratory since 1970.^{21,22} The method and clinical application have been well-documented by us as well as by other investigators.^{23,24} This simple procedure depends on the identification of a prominent and fairly consistent collateral arterial pathway between the external carotid artery and a hemodynamically compromised internal carotid artery (Figure 1). A small ultrasound flow probe identifies the supraorbital artery, and the changes in its flow characteristics are noted subsequent to digital occlusion of the superficial temporal artery (Figure 2). Normally, supraorbital artery flow will increase after this maneuver. With internal carotid artery occlusive disease, however, flow is reduced to a pronounced degree or absent. The test is noted as being either positive (an abnormal flow response) or negative (normal flow response).

The oculopneumoplethysmography test described by Gee and co-workers directly records the ophthalmic artery pulse from which ophthalmic artery blood pressure can be ascertained by an analogue method.²⁵⁻²⁷ Two hemispheric paralimbal suction cups are connected to the patient's eyes and to separate transducers by means of flexible tubing (Figure 3). By using a vacuum pump, a negative pressure of 300 mm of mercury is applied which serves to adhere the cups to the sclerae. The vacuum is then reduced to atmospheric pressure in a linear fashion over 25 seconds. The



Figure 3.—Oculopneumoplethysmography test being done.

pulse pressure alterations are superimposed on this calibrated pressure range, transmitted to the transducers, and then visualized on a strip chart recorder tracing, creating a pressure-dependent deflection for each eye. At a vacuum pressure of 300 mm of mercury, a deflection recorded from the transducer corresponds to an internal carotid artery pressure of 110 mm of mercury²⁸ (Figure 4). Ophthalmic artery pressures assessed by the Gee oculopneumoplethysmography method average 70 percent of the simultaneously recorded brachial artery pressure with a range of 60 percent to 95 percent. Criteria have been established for interpreting the results of this test that achieve a 97 percent accuracy in identifying a hemodynamically significant lesion in the internal carotid artery system. When these tests show an abnormality in flow or pressure, the accuracy is such that it can be assumed that a lesion of hemodynamic significance exists in the internal carotid artery system. Angiography should be undertaken, and if the angiogram confirms the diagnosis and further shows that the lesion is amenable to surgical correction, this modality of therapy should be seriously considered, for we have now shown a smaller subgroup of the "asymptomatic bruit" population—that is, those with an asymptomatic hemodynamically significant lesion. Although never studied in great detail, intuitively it can be assumed that we are dealing here with patients who are at highest risk of sudden stroke (Figure 5).

Transient Ischemic Attacks

Transient ischemic attacks or little strokes occur frequently among older persons, generally carrying a dire prognosis²⁹⁻³¹ (Figure 6). Because the symptoms are usually quite characteristic, they tend to be readily diagnosed.³² Amaurosis fugax—or painless, transient, monocular blind-

ness—is a typical symptom, often described as a “shade coming down over one eye” or a “shutter closing,” first graying the vision, then leading to total blindness, after which vision usually returns within 30 to 60 seconds. This symptom is one of the pathognomonic indicators of carotid artery disease.³³ A variable number of persons in this group will experience recurrent attacks and then progress to complete monocular blindness with retinal ischemia and infarction. The incidence of subsequent cerebral hemispheric stroke is about the same in this type of symptom complex as for other types of transient ischemic attacks. In a study of 70 such patients, 96 percent of the angiograms indicated atherosclerotic lesions at the appropriate carotid bifurcation.³³ In a similar age group, asymptomatic irregularity at the carotid bifurcation could be expected in about 25 percent of patients.³³ Episodes of transient ischemia are usually manifestations of an ulcerating, embolizing atherosclerotic plaque. Although attacks of retinal ischemia have been attributed to a known cardiac embolic source in 10 percent to 12 percent of cases, focal cerebral ischemia is uncommon from a cardiac source.

In addition to amaurosis fugax, a wide spectrum of transient neurologic dysfunctions develop, referred to as TIA's (transient ischemic attacks). Among the most typical are unilateral weakness, paresthesias or sensory loss, usually lasting a few minutes but occasionally persisting up to 24 hours and involving either the arm or the leg. Intermittent difficulty in speech or written communication as well as intermittent severe ataxia or severe episodic double vision are also frequent manifes-

tations of transient cerebral ischemia. Episodic dimness of vision or bilateral loss of vision with recovery over 2 to 30 minutes is often reported.

Occasionally the syndrome resembles the distribution of a specific arterial supply. These should be recognized even though the anatomic site of a lesion cannot be predicted on the basis of the symptom complex. Through the years this disquieting observation has caused considerable confusion. Middle cerebral artery symptoms tend to result in a hemiplegia, hemihypesthesia, hemianesthesia, or homonymous hemianopia. Aphasia, dysphasia, and hemiparesis also signify middle cerebral artery transient ischemia attacks. Anterior cerebral artery symptoms usually present as weakness of the lower extremity (but not of the upper extremity). Mental changes may range from mild to frank dementia, dyspraxia and apraxia. Vertebrobasilar symptoms typically accompany abnormalities of motor function such as weakness, clumsiness or paralysis of one or more extremities up to and including quadriplegia. Vertigo, nystagmus, and bilateral sensory or motor loss associated with palsies of cranial nerves three to nine are also indicative of vertebrobasilar insufficiency. In addition, bilateral homonymous hemianopia, ataxia, imbalance, unsteadiness and disequilibrium are frequently seen in attacks of vertebrobasilar insufficiency.

Although the symptoms may be typical of a particular arterial distribution, it should be reiterated that anatomical localization on the basis of symptom complex alone is apt to be misleading. In one cooperative study, 57 percent of the patients thought definitely to have vertebrobasilar

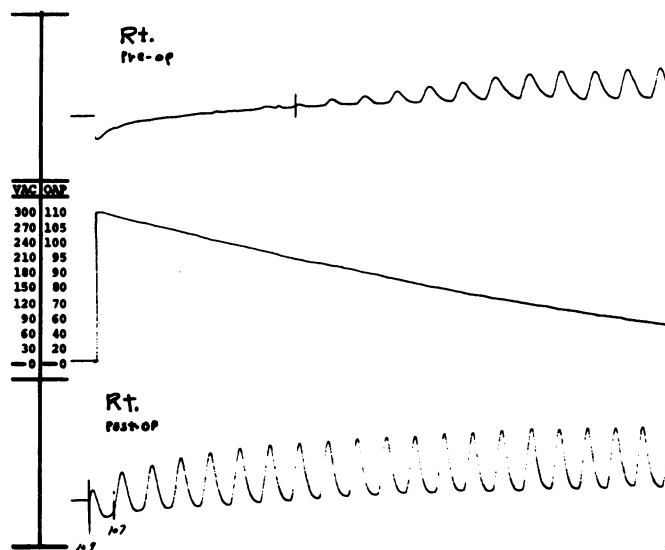


Figure 4.—Oculopneumoplethysmographic wave tracing on a 57-year-old patient showing (above) a hemodynamically significant lesion in the right internal carotid artery that caused recurrent attacks of transient left hemiparesis, and (below) a normal wave pattern after internal carotid endarterectomy, which was followed by relief of symptoms. The sloping line between the two tracings indicates the decline in vacuum in the scleral cups. The point on the slope at which the pressure wave first appears can be used to calculate the ophthalmic artery pressure by use of the analogue ruler on the left-hand side of the tracing.

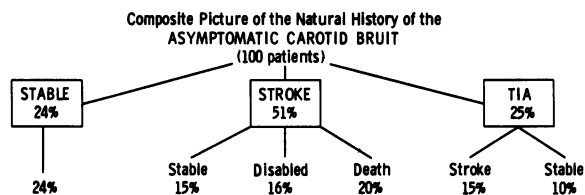


Figure 5.—Probable outcome of an asymptomatic carotid bruit (composite picture from several epidemiologic studies).

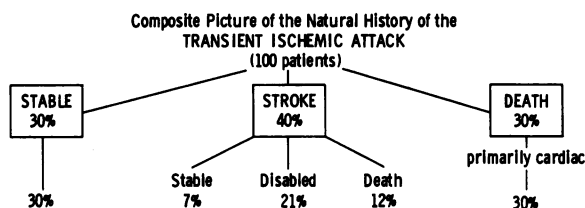


Figure 6.—Probable natural history of a cerebral transient ischemic attack.

transient ischemic attacks were angiographically shown to have only unilateral or bilateral carotid lesions.¹⁵ In the evolution of the atherosclerotic lesion, one or more of various collateral pathways may develop. The ischemic symptoms may occur in the anatomic site closest to the lesion, or farthest from the lesion if stenosis develops in the collateral artery supplying the distribution of an occluded vessel.

Several other important clinical features of transient ischemic attacks become evident through epidemiologic studies. An aspect of transient ischemic attacks which has proven to be equally as disconcerting as the problem of anatomical localization is the inability to ascribe the symptom complex to a specific type of occlusive lesion. An ulcerated, embolizing, but nonobstructing plaque, a stenotic hemodynamically significant plaque and a totally occluded internal carotid artery may all present with the same symptom complex.⁸⁴ We have observed patients evolve through documented ulcerated plaque embolization, stenosis and then occlusion without change in the characteristics of the TIA.²² About 25 percent of patients with carotid transient ischemic attacks will have a totally occluded vessel on the appropriate side at the time of initial investigation. Patients in whom a total occlusion of the carotid artery develops during the period of observation will have a 33 percent chance of continuing to have transient ischemic attacks in the same distribution.

One fact, however, remains fairly consistent: when any of the symptom complexes are encountered, there is a high probability that a lesion will

be found in the extracranial cerebrovascular system. Although, as previously noted, attacks of retinal ischemia have been attributed to a known cardiac source of emboli (in 10 percent to 12 percent of the cases), focal cerebral ischemia is uncommon from cardiac embolization and extremely uncommon in cardiac dysrhythmia.⁸⁵ Episodes of cardiac dysrhythmia are far more likely to result in transient episodes of dizziness or syncope than the focal characteristics of carotid embolization.⁸⁶

Unquestionably, the natural history and the implication for development of stroke are the most important issues in dealing with a patient having transient ischemic attacks. The attacks per se usually prove to be inconsequential, and information about them often can be elicited in history-taking when a patient presents with a completely unrelated problem.^{18,19,29}

A number of epidemiologic studies have shed light on the fate of patients with attacks of transient cerebral ischemia, and although they vary, depending on the type of population surveyed and the associated risk factors encompassed by that population, a fairly consistent pattern is readily discernible. In one study, for example, more than 60 percent of patients with transient ischemic attacks progressed to a completed stroke within a mean period of 4.6 years.^{4,81} In a multicenter study reported by Fields, strokes occurred in 18 percent of the patients within the four-year observation period.³⁷ Two other important risk indicators were identified. First, in patients over 65 years of age, 50 percent went on to stroke or further episodes of transient cerebral ischemia during this short follow-up period. Second, in patients who had a single transient ischemic attack there was a 14 percent incidence of subsequent stroke, whereas those with multiple transient ischemic attacks had a 45 percent incidence of stroke within the same observation period.⁸⁷ In one of the most carefully controlled epidemiologic studies, encompassing a relatively stable population in Minnesota that was followed over a 20-year period,³⁸ frank hemiplegic stroke occurred in 36 percent of the patients during the period of observation. In 51 percent of these patients the neurologic event occurred in the first year, and in 21 percent during the first month. This represented more than 15 times the anticipated stroke occurrence in an age-matched population.

That a person with a transient ischemic attack

is at high risk for stroke seems beyond question.^{17,39} An evaluation of such a patient is predicated on the need to establish the diagnosis beyond reasonable doubt and establish the location of the lesion anatomically. If, as in most instances, the lesion is situated at the carotid bifurcation, it is important to establish whether the lesion is a nonobstructing but embolizing plaque, or an obstructing, hemodynamically significant lesion. Examination of the carotid pulses and auscultation for bruits are essential, inasmuch as the site of origin of the transient ischemic attack and the bruit correlate in 60 percent of the cases.⁴⁰ Noninvasive pressure and flow tests of cerebrovascular function are useful in localizing the lesion, helping to interpret the angiogram when multiple lesions are present, and enabling a follow-up evaluation of the patients whether they are treated medically or surgically. If the noninvasive studies do not indicate a hemodynamically obstructing lesion, it is likely that an embolizing plaque is present and the patient may benefit from antiplatelet therapy. Although determining the precise anatomic location is not necessary for effective antiplatelet therapy, it has been our practice to advise angiographic investigation in all patients with transient ischemic attacks in order to ascertain the status of the cerebral vascular circulation before instituting either medical or surgical therapy.

Concomitant with the evolution of diagnostic tests to assess the prestroke lesions more accurately has come the development of new, highly effective prophylactic medical regimens.

Medical Therapy

Medical therapy has a long history encompassing carefully controlled clinical trials and sporadic reports of anecdotal experience.⁴¹⁻⁴⁵ The benefits of reducing hypertension, decreasing hyperlipidemia, and controlling diabetes with diet or insulin are manifold; reduction in stroke risk is only one of the benefits. Anticoagulant therapy has undergone considerable trial, and although it has achieved great benefit in protection from embolization of cardiac origin, valvular disease, atrial fibrillation and prosthetic valves, there has been no success in treating thromboembolic stroke from other causes. Moreover, significant morbidity and mortality have ensued as a result of hemorrhagic complications.^{42,45,46} The recognition that embolization of platelet aggregates represents the prevailing cause of transient ischemic attacks

and stroke has focused attention on the possibilities of antiplatelet therapy.⁴⁷⁻⁵² Platelet aggregates form the chief thromboembolic material in the arterial circulation and have been shown in the cerebral circulation subsequent to TIA and stroke, as well as in the retinal circulation following episodes of amaurosis fugax.^{34,51-54} In atherosclerotic disease of the extracranial cerebrovascular system, ulcerations of the diseased intima can frequently be shown, particularly in areas of turbulence such as the carotid bifurcations.⁵⁵ At the time of operation in cases of recurrent transient cerebral ischemia attacks, these ulcerations have been seen to contain fresh clumps of platelet aggregates.^{51,55} Even in occlusive lesions, ulcerations can be seen distal to the stenosis where the jet of blood strikes the intima, and normal laminar flow is disorganized. It is likely that even in stenotic hemodynamically significant lesions many episodes of transient cerebral ischemia are secondary to embolization rather than to transient interruption of cerebral perfusion.

When intimal ulceration develops, collagen fibers of the arterial media are exposed. Collagen is a potent platelet aggregating agent, both *in vivo* and *in vitro*. Platelets coming in contact with exposed collagen undergo a change in the cell surface membrane which causes the platelets to adhere to the collagen substrate and leads to platelet degranulation, releasing platelet factors into the surrounding blood. This "release reaction" of the platelets is followed by further platelet aggregation and augmentation of the release reaction, much as the cascade effect of blood coagulation accelerates thrombosis in the venous circulation. Although the platelet aggregate is stabilized by fibrin, the shear forces of the blood are such that fragmentation and embolization are characteristic sequelae; with the cycle of embolization, exposure of collagen, reaggregation of platelets and then reembolization forming a typical clinical cycle. As platelet aggregation and release take place, the granules release vasoactive amines and other coagulation substrates into the surrounding blood. Prostaglandin biosynthesis is initiated, and this results in the synthesis of thromboxane A₂ which is both a potent aggregating agent and the strongest naturally occurring vasoconstricting amine. Although quite labile, with a half-life of 32 seconds, this factor is probably most important in generating a transient ischemic attack when the area of transient ischemia (such as the middle cerebral artery distribution) tends to be out of

proportion to the probable size of the embolizing aggregates, and indeed, angiographic evidence of major vascular obstruction is rarely obtained.

The effect of thromboxane A_2 on the cerebrovascular system has been well shown, and although it is an effective constrictor of both coronary and renal arteries, its effect is greatly augmented on cerebral vessels. For example, thromboxane A_2 has been shown to be at least ten times more powerful than 5-hydroxy-tryptamine or PGF_2 alpha on the cerebral vessels. Under experimental conditions, thromboxane B_2 , the metabolic product of thromboxane A_2 , is found in large quantities in brain tissue after vasospastic episodes, suggesting that thromboxane A_2 may also be produced intracerebrally.⁵⁶

The biochemical reactions involved in this process have been carefully documented^{47,57-59} (Figure 7). When platelets come in contact with collagen, phospholipids in the platelet membrane are acted upon by phospholipase, producing arachidonic acid. The reaction of arachidonic acid to the cyclic endoperoxides, PGG_2 and PGH_2 is mediated by a cyclooxygenase, prostaglandin synthetase. The cyclic endoperoxides are further metabolized to thromboxane A_2 , and thence to the stable end-product, thromboxane B_2 . The endoperoxides also proceed to form PGE_2 , PGF_2 alpha, and PGD_2 .⁵⁹ Review of these metabolic pathways

is critical to understanding the appropriate medical therapy and the action of various drug protocols. Of the known pharmacologic agents that affect platelet function, acetylsalicylic acid, dipyridamole and sulfinpyrazone have been given extensive clinical trials.^{12,43,47-52,57,58,60} Aspirin has a specific effect on the platelet because it acts to acetylate the cyclooxygenase which mediates the conversion of arachidonic acid to the cyclic endoperoxides which are the prostaglandin precursors. Once a platelet's membrane cyclooxygenase is acetylated, the platelet ceases to function normally for the duration of its circulatory life. The reaction is irreversible, and it is therefore possible with one dose of aspirin to acetylate the cyclooxygenase of all of the circulating platelets, which have an average life span of ten days. Platelet function will then return to normal at the rate of 10 percent each day. In an average patient, a dose of 10 grains of aspirin will effect this acetylation, although there is some variability that can best be assessed by platelet function tests such as collagen and epinephrine-stimulated aggregation.⁴⁷ Sulfinpyrazone is a reversible, competitive inhibitor of cyclooxygenase activity and its effects can be overcome by strong aggregating stimuli which can then generate high concentrations of arachidonic acid. The effect of dipyridamole is to raise cyclic adenosine monophosphate stabilizing the

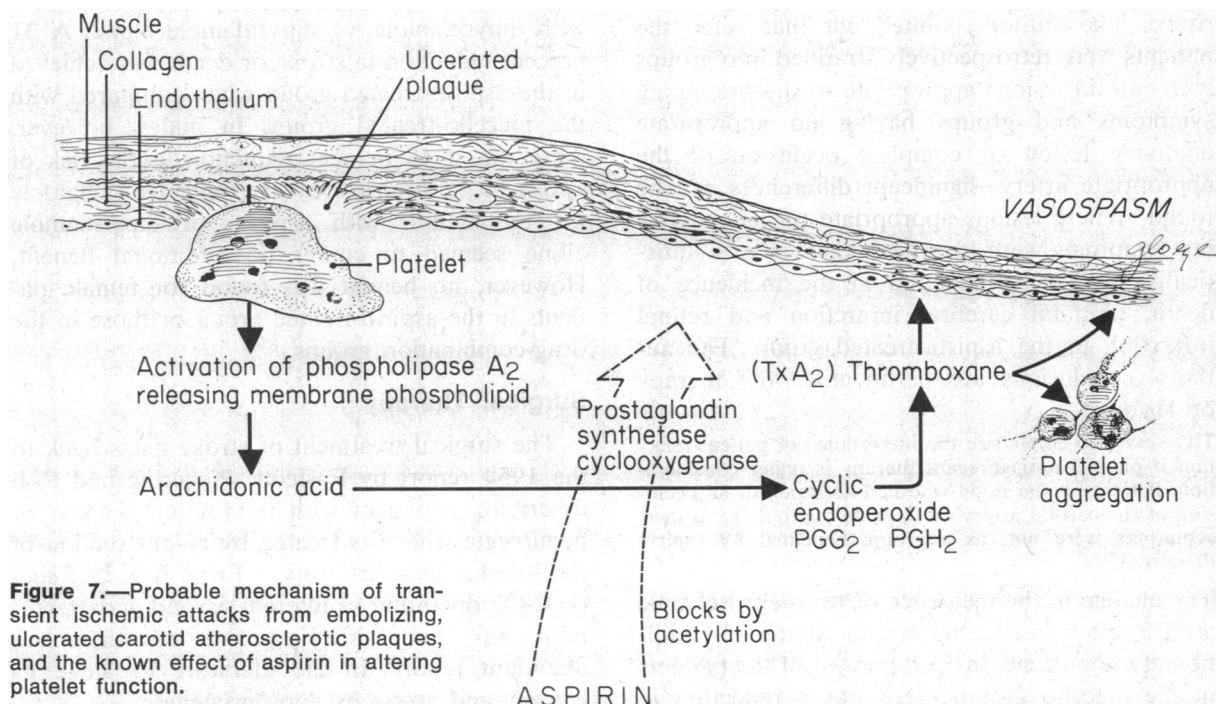


Figure 7.—Probable mechanism of transient ischemic attacks from embolizing, ulcerated carotid atherosclerotic plaques, and the known effect of aspirin in altering platelet function.

platelet membrane, and interfering with platelet aggregation and the release reaction. The effect of dipyridamole lasts a maximum of four to six hours, after which platelet function returns to normal.

Early reports of the United States Multicenter studies on the effects of aspirin on cerebral ischemia are now available for analysis.^{48,61} When the endpoints of stroke or death were considered, there was unfortunately no significant difference between the groups that took aspirin and the group that had the placebo. If certain subgroups are separated out, however, important information regarding the therapy of transient ischemic attacks may be obtained. There was substantial protection from stroke and death if the groups were subdivided into those that had an "appropriate" lesion compared to those who had an "inappropriate" lesion. When an ulcerated plaque occurred in the vessel supplying the symptomatic hemisphere, there was a 13.8 percent incidence of stroke or death in the aspirin-treated group compared with a 43.1 percent incidence of stroke or death in the group taking the placebo, a statistically significant difference. If the lesion was inappropriate—for example, carotid occlusion where embolization is unlikely—there was a 35 percent incidence of stroke or death in the aspirin-treated group compared with a 47 percent incidence of stroke or death in the group receiving placebo, a difference having no statistical significance. The authors pointed out that when the patients were retrospectively stratified into groups with carotid lesions appropriate to the presenting symptoms and groups having no appropriate anatomic lesion or complete occlusion of the appropriate artery, significant differences can be found. Where lesions appropriate to the presenting symptoms were identified, there was a statistically significant reduction in the incidence of death, nonfatal cerebral infarction and retinal infarction in the aspirin-treated group. The authors' conclusions are pertinent to the therapy of TIA's:

This serves to emphasize the importance of patient selection if platelet antiaggregant therapy is under consideration. Patients in the study who had no lesion or an occlusion of the carotid artery on the side appropriate to their symptoms were not, as a group, benefited by aspirin therapy.⁴⁸

The change in the incidence of transient ischemic attacks after instituting aspirin therapy is additionally important. In 55.8 percent of the patients in the placebo group, there was a reduction in

frequency of transient ischemic attacks or no further attacks occurred. In the aspirin-treated group there was an 80.8 percent reduction in the frequency of or complete ablation of transient ischemic attacks. The hazard underlying this observation is that transient ischemic symptoms can be masked in a patient in whom there is a progressing stenotic lesion which will nevertheless result in a thrombotic stroke. Therefore, careful surveillance should be maintained in patients who are treated with antiplatelet regimens to make sure that the ulcerated lesion does not progress to one of hemodynamic significance, in which case it should be treated surgically before thrombosis occurs. Indiscriminate treatment of patients with aspirin or other antiplatelet drugs may have undesirable sequelae, inasmuch as the interference with prostaglandin synthesis also blocks the formation of prostacyclin, a potent vasodilating agent with strong antiplatelet actions, produced by vascular endothelial cells. Prostacyclin prevents platelet adhesion and thrombosis on normal arterial endothelium. In a Canadian multicenter study covering 5½ years, aspirin in a dose of 1,300 mg per day was found to protect men in whom transient ischemic attacks had occurred from subsequent stroke or death.¹² The Canadian study analyzed 585 patients who had transient ischemic attacks and were randomly allocated into four treatment groups, each of which took one of the following: placebo, aspirin, aspirin with dipyridamole, or dipyridamole alone. A 31 percent reduction in stroke or death was achieved in the aspirin-treated group when compared with the placebo-treated group. In males, however, there was a 48 percent reduction in the risk of stroke in the aspirin-treated group. Dipyridamole in combination with aspirin, or dipyridamole alone seemed to confer no additional benefit. However, no benefit was found for female patients in the aspirin-treated group or those in the drug-combination groups.

Surgical Therapy

The surgical treatment of stroke dates back to the 1954 report by Eastcott, Pickering and Rob describing a patient with intermittent attacks of hemiplegia who was treated by reconstruction of the internal carotid artery.⁶² From that first success, the operation of internal carotid endarterectomy has been widely applied and there are abundant reports in the literature to judge its efficacy and assess its appropriateness.

It has become quite evident that carotid endarterectomy is inappropriate in the treatment for an acute stroke or for the relief of a fixed or evolving neurologic deficit. Disobliteration of an already thrombosed internal carotid artery is likewise usually ineffective. However, when a hemodynamically significant obstructing lesion, or an ulcerating plaque, is encountered which remains symptomatic despite adequate medical therapy, or when a successfully treated ulcerated plaque progresses to the point of hemodynamic obstruction, carotid endarterectomy provides an effective treatment modality. Although relatively simple, safe and effective, this procedure nevertheless demands meticulous operative technique and familiarity with the myriad problems associated with cerebrovascular disease. Analyzing the results of carotid endarterectomy can be a fascinating adventure into the realm of surgical competence. The individual variations often hidden in multicenter trials are easily discerned in the multiple individual and large center results which have been individually published.⁶³ Morbidity and mortality rates range from none to a high of 25 percent, a rather disconcerting spread, indicating that when surgical correction of these lesions is contemplated, a specialized vascular surgical facility be chosen with care.

The surgical therapy of stroke is prophylactic and therefore depends largely on diagnostic confidence and thorough knowledge of the epidemiology of asymptomatic bruits and transient ischemic attacks. In treating patients with asymptomatic occlusive lesions or transient ischemic attacks, the operation can be carried out with an operative mortality less than 1 percent and morbidity less than 0.5 percent.¹⁶ In a series encompassing over 2,000 patients reported by Rob on a subgroup of 103 patients followed for more than five years, 83 percent remained asymptomatic, one patient died within 30 days of operation, an additional five patients died from strokes and 25 patients died as a result of myocardial infarction during the follow-up period.⁶⁴ Incidence of transient neurologic deficit in this group was 3 percent. Thompson, reporting on over 1,000 patients during a 19-year period, indicated an operative mortality of 1.5 percent, which could be subdivided into an operative mortality of 4.2 percent for frank strokes (a condition for which carotid endarterectomy is no longer recommended), a mortality of 0.8 percent for patients with transient ischemic attacks, and no mortality for those with

asymptomatic carotid bruits. In 0.7 percent of cases there was some permanent neurologic deficit postoperatively. In the patients with unilateral stenotic lesions and contralateral occlusion, there was no mortality and only a 0.8 percent incidence of neurologic deficit.¹⁶

In patients with transient ischemic attacks on the ipsilateral side to a complete internal carotid artery occlusion, the presence of stenosis at the external carotid artery orifice must be investigated. The ipsilateral external carotid artery is a major collateral pathway in the presence of internal carotid artery occlusion and contributes significantly to cerebral perfusion. In a patient who has an asymptomatic internal carotid artery occlusion, transient ischemic attacks may begin to develop in that hemisphere when a stenotic plaque develops at the external carotid artery orifice; in a significant number of cases the symptoms will be alleviated by external carotid endarterectomy.

Analysis of the data published on the United States Multicenter Trial of aspirin therapy in cerebral ischemia provides valuable information regarding anticipated benefits from medical and surgical therapy. Relatively homogeneous groups were treated at large medical centers where the emphasis was on competent treatment of cerebrovascular disease.^{48,61} In patients assigned to the medical therapy arm of the protocol, a 20-percent incidence of stroke or death occurred within six months of entry into the study, whether the patient was given aspirin or a placebo. Of the 178 participants in that group, 25 had had a thrombotic stroke (14 percent); in 18 of these patients, the stroke occurred on the same side as the original symptoms (10 percent of the entire group). Looked at another way, 72 percent of the patients who had a stroke during the study, regardless of whether they were receiving aspirin or placebo, had the stroke on the side of the symptomatic lesion. In all of these patients, angiographic evaluation had been carried out. Of 130 patients who were assigned to the surgical arm of the protocol, 16 died within two years of follow-up, irrespective of whether the patient was taking aspirin or placebo, a mortality rate of 12.3 percent. Strokes occurred in ten patients (7.6 percent), three of these occurred on the operated side (30 percent). Unfortunately, no strict criteria were developed or adhered to when selecting patients for surgical or medical therapy, inasmuch as the study was designed to assess the effect of

aspirin versus placebo regardless of antecedent therapy. Allocation to surgical therapy and then the treatment protocol was made by the medical and surgical consultants of each medical center. There is, however, a striking difference between the two groups in the overall incidence of stroke (7.6 percent compared with 14 percent). This further underscores the need to assign patients carefully to the proper treatment regimen at the outset, reassessing their progress and modifying the treatment program if the results are unsatisfactory.⁶⁵

A new operative approach has greatly increased the potential number of patients who may benefit from correction of cerebrovascular obstructive disease. These are patients whose cerebral circulation is seriously compromised owing to obstructing lesions that are considered inaccessible to direct surgical correction: (1) patients having transient hemispheric ischemic attacks with occluded ipsilateral internal carotid artery and a normal or enlarged external carotid artery without stenosis, (2) patients having transient ischemic attacks with stenosis of the intracranial internal carotid artery, particularly at the area of the carotid siphon and (3) patients having transient ischemic attacks with stenosis of the middle cerebral artery. The microvascular anastomosis of superficial temporal artery to middle cerebral artery originally reported by Yasargil⁶⁶ bypasses the entire internal carotid artery, augmenting the usual external to internal carotid artery collateral channels by direct anastomosis of the normal external carotid artery system, into the intracranial circulation by way of the middle cerebral artery. As experience with this procedure increases, its safety and effectiveness appear to improve and become better established. Of the patients with patent anastomosis, 80 percent have been reported free of symptoms, and the early occlusion rate is about 10 percent.⁶⁷ This operation is currently undergoing a multicenter trial.

Summary

Stroke is a prevailing cause of serious morbidity and mortality in the entire Western world. Its cost to patients and society makes it one of the most devastating illnesses suffered by mankind. Although the means of modifying the course of events once the stroke occurs still remain elusive, we have achieved progress in identifying and treating stroke-prone patients. Patients with asymptomatic cervical bruits as well as those having

transient ischemic attacks represent a particularly high-risk group for stroke. In a patient with an asymptomatic cervical bruit, noninvasive cerebrovascular testing should be done, and if the tests show a high likelihood of a hemodynamically significant lesion in the internal carotid artery system, angiography should be carried out to define the anatomic position, extent and character of the lesion so that a rational therapeutic protocol can be planned. If there is an ulcerated, nonobstructing lesion in a male patient, therapy should be instituted with aspirin or aspirin combined with persantin. Unfortunately, no satisfactory medical therapy has yet been shown for female patients.

Patients who are managed medically should be carefully watched and reevaluated at six-month to yearly intervals to ascertain whether the bruit has altered in character or whether the noninvasive tests indicate hemodynamic change. It is important to realize that adequate medical therapy can mask symptoms in a lesion that may be progressing to occlusion, and if this occurs surgical intervention should be undertaken. In patients with documented transient ischemic attacks, baseline noninvasive tests should be done so that therapy and progress can be carefully followed up without requiring repetitive angiography. However, initial angiography is highly useful in this group of patients, regardless of the type of therapy employed. The patient's case is then followed at six-month to yearly intervals, depending on the clinically assessed aggressiveness of the general atherosclerotic process. If the noninvasive tests indicate signs of hemodynamic change, operative intervention should be contemplated. If transient ischemic attacks occur, platelet function studies should be repeated, and if platelet function has not altered, the patient should be reinstructed in drug compliance and the dosage increased. If transient ischemic attacks persist despite adequate platelet suppression, operative intervention should be planned, even in cases of nonobstructing ulcerated plaque.^{55,68}

If the lesion is stenotic, and if it is greater than 60 percent of the cross-sectional diameter and surgically accessible, it should be treated operatively. If an obstructing lesion is found, successful operative correction of the lesion will provide the best protection against stroke. Patients with a completed stable stroke whose function has significantly improved but who have an extracranial cerebrovascular lesion should be treated as described above, depending on the nature of the

lesion. Although no improvement in the completed stroke is likely, the risk of a new stroke is so high that it jeopardizes the earlier recuperation.³⁹

Substantial progress will undoubtedly be made with respect to noninvasive diagnosis and medical therapy, as well as evaluation of newer operative techniques such as the middle cerebral artery to superficial temporal artery bypass. Nevertheless, we now have tools to begin controlling this difficult problem. Our next step must take us beyond investigation and clinical trials to widespread, intelligent application of the diagnostic and therapeutic principles that have been established.

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